

## PD3-1-8

## Novel Therapeutics, Thu, 12:30 - 14:15

**Motexafin Gadolinium (MGd) is active as a single agent in advanced non-small-cell lung cancer (NSCLC) patients who failed platinum-based chemotherapy: preliminary results of a phase II trial**

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**Background:** Motexafin gadolinium (MGd) is a tumor-selective antineoplastic agent that disrupts redox dependent pathways by targeting oxidative stress-related proteins such as thioredoxin reductase (TRX). TRX often is overexpressed in NSCLC and is associated with a poor prognosis. Inhibition of TRX reverses tumor phenotype in lung carcinoma cells in vitro and in vivo. This randomized 2-stage phase II trial investigated tumor response and survival with 2 regimens of single agent MGd for the 2nd line treatment of advanced NSCLC.

**Methods:** Patients with locally advanced or metastatic NSCLC ± brain metastases, ECOG PS 0-1, who had received one prior platinum-based chemotherapy regimen ± kinase inhibitor were randomized to intravenous MGd (10 mg/kg/week - Group A) or MGd (15 mg/kg/q 3 weeks - Group B) given in 21 day cycles. The sample size was 30 per arm in stage 1, and 24 per arm in stage 2. Response was evaluated by RECIST every 6 weeks.

**Results:** 56 evaluable patients, median age of 62 years (range 41-85), with locally advanced (16%) or metastatic (84%) adenocarcinoma (46%), squamous cell carcinoma (16%), large cell carcinoma (9%), bronchoalveolar carcinoma (4%) or other NSCLC (25%) were randomized to group A (N=26) or group B (N=30). 38% had not responded to first line chemotherapy. MGd treatment was well tolerated, with 1-12 cycles (median 2, mean 3) administered. The most common MGd related grade 3+ adverse events were hypophosphatemia (17.9%), fatigue (12.5%), finger blisters (5.4%) and rash (5.4%). 53 patients were evaluable for response, with a response rate of 5.7% (3 PR, 2 in Group A, 1 in Group B), and 37.7% stable disease. Median time to progression was 12 weeks with 41% free from progression > 1 year. Median survival of 56 evaluable patients was 10.2 months (95% CI: 6.7 months - not reached), with 1-year survival of 44%. Median survival for Group A is not reached at > 14 months, and 9.2 months for Group B.

**Conclusions:** MGd appears active as a single agent for second line treatment of NSCLC patients with advanced or metastatic NSCLC who have failed prior platinum-based chemotherapy, with a response rate comparable to other approved agents, promising survival, and a favorable safety profile. The trial has met the criteria for continuation into stage 2 for each treatment group.

## PD3-2-1

## Molecular Targeted Therapy: EGFR inhibitors, Thu, 12:30 - 14:15

**Pharmacokinetics of gefitinib predicts the antitumor activity for advanced non-small cell lung cancer (NSCLC)**

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**Background:** Little is known about the relationship between the pharmacokinetics and efficacy of gefitinib.

**Methods:** Plasma trough levels of gefitinib were measured on days 0, 3 (D3), and 8 (D8) by HPLC in advanced NSCLC patients treated with gefitinib 250 mg daily. Eligibility criteria included: performance status (PS) ≤ 3, age ≤ 80, stage IIIB-IV, and written informed consent.

**Results:** Fifty patients were enrolled, and 44 patients were assessable. The median [25%-75%] values of D3 and D8 was 662 [440-937] and 1064 [782-1405] ng/ml, respectively. D8/D3 rate was categorized by 1.587 of the median value. In 44 patients, the median time to progression (TTP) was 83 days, and the median overall survival (OS) was 224 days. The differences in TTP were compared by Kaplan-Meier method and log-rank test: D8/D3 (high D8/D3, median 209 days vs. low D8/D3, 43 days;  $P = 0.0229$ ), smoking (never-smokers, 224 days vs smokers, 32 days;  $P = 0.0467$ ), and histology (adenocarcinoma, 97 days vs. non-adenocarcinoma, 27 days;  $P = 0.0096$ ). Sex, age, PS, previous treatments, and the use of antacids were not significant. Multivariate analysis showed that TTP was associated with D8/D3 (hazard rate, 95%CI; 0.458, 0.234-0.898) and smoking (2.005, 1.030-3.903). Never-smokers with high D8/D3 showed the best TTP, and smokers with low D8/D3 showed the worst TTP. Never-smokers with low D8/D3 and smokers with high D8/D3 showed similar TTP curves. In contrast, OS was associated with smoking (hazard rate, 95%CI; 3.182, 1.506-6.724), but not D8/D3.

**Conclusions:** High D8/D3 was independently associated with better TTP in gefitinib-treated NSCLC patients. Our findings suggest that pharmacokinetics of gefitinib may be involved in its anti-tumor activity.

## PD3-2-2

## Molecular Targeted Therapy: EGFR inhibitors, Thu, 12:30 - 14:15

**Changing the natural history of advanced non-small cell lung cancer with gefitinib? A single-center experience in Korea**

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**Background:** Gefitinib (ZD1839, Iressa<sup>TM</sup>), one of the oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors has favorable response in subgroups of patients, especially in Asian population. It also has been reported that the IRESSA Survival Evaluation in Lung Cancer (ISEL) phase III trial showed significantly longer survival in the gefitinib group than the placebo group for never-smoker and patients of Asian origin. Gefitinib was available in Korea since 2002, therefore in this study we compared the overall survival in patients with advanced non-small cell lung cancer (NSCLC) between pre-gefitinib and post-gefitinib eras.

**Methods:** Between January 1999 and December 2005, a total of 805 patients with advanced/metastatic or recurrent NSCLC who were treat-